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08/488,164	06/07/95	KOPCHICK J	7707-015

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EXAMINER	
SAOUD, C	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/488,164	Applicant(s) KOPCHICK et al.
	Examiner Christine Saoud	Group Art Unit 1646

☒ Responsive to communication(s) filed on *Nov 8, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *10-45, 62, 63, and 65-74* is/are pending in the application.

Of the above, claim(s) *45* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *10-44, 62, 63, and 65-74* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's second submission after final filed on 08 November 1999 has been entered.

Applicant's request for an interview is noted but could not be granted in the time frame desired because upon the filing of a response to the previous Office action, the PTO is required to issue an action within 2 months. Additionally, once a response has been filed, the PTO must respond to the submission and it is not clear what use an interview will have when Applicant has already presented its arguments in writing. These arguments must be responded to in writing, thus an interview is not warranted. If Applicant would like to interview the instant application, it is suggested that a request be made after receiving this Office action and before filing the next response. The request should be made telephonically to either the Examiner of record or to the Supervisory Patent Examiner if the Examiner of record cannot be reached.

Response to Amendment

2. Claim 29 has been amended and claim 74 have been added as requested in the amendment of paper #21, filed 08 November 1999. Claims 10-45, 62-63 and 65-74 are pending in the instant application. Claim 45 remains withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed 08 November 1999 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 112

6. Claims 10-44, 62, 65-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to subject matter of "a purified or non-naturally occurring DNA molecule" encoding a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which (A) is at least 50% identical with the amino acid sequence of a first reference vertebrate hormone". However, the instant specification fails to provide basis for many of the claim limitations which define the "purified or non-naturally occurring DNA molecule" of the claims. First, the instant specification does not contemplate the

invention of a polypeptide derived from a first reference vertebrate hormone. The instant specification is directed to "proteins which are substantially homologous with a vertebrate GH but have growth-inhibitory activity" (see specification at page 6, lines 35-37). Specifically, the specification is directed to the mutation of the amino acid in vertebrate growth hormones which corresponds to Gly-119 in bovine growth hormone (see page 7 of the specification). Additional mutations contemplated in the instant specification are at amino acid positions 115, 117, 119 and 122 of bovine growth hormone (see page 11 of the specification). The specification does not contemplate variant proteins which have an amino acid sequence at least 50% identical with the sequence of a "first reference vertebrate hormone" as recited in the claims. The specification states at page 14, lines 12-15 that "the GH antagonist comprises an alpha helix having an amino acid sequence homology of at least 50% with the third alpha helix of a vertebrate GH, especially bGH or hGH". This is not the breadth and scope as what is claimed and it does not naturally flow from the disclosure of the instant specification. Additionally, the instant specification does not provide for further claims to percent identity of 66%, 80% and 90% identity with the sequence of a first reference vertebrate hormone (see claims 14, 15, 18, 30-32, 70-72). The specification identifies that there is homology of other mammalian growth hormones with bovine growth hormone, (66% for human, see page 14 of the specification), but this is not a basis for a claim to a variant polypeptide which has 66% identity to a reference hormone. The inventive concept of such is not conveyed by the disclosure that human growth hormone is 66% homologous to bovine growth hormone.

The claims are also include limitations relating to binding affinity for "the first reference hormone's receptor" and the limitation of "at least 10% of the binding affinity of the wild-type first reference hormone for that receptor" (see claims 10, 35, 62, 66) . However, no basis in the specification could be found for this % binding affinity or for using any other type of receptor other than the growth hormone receptor. This is because the specification only contemplates growth hormone variants which bind to the growth hormone receptor, absent evidence to the contrary.

Claim 19 is directed to molecules wherein non conservative substitutions are at all of the residues other than those belonging to particular domains recited in the claim. There does not appear to be a basis in the specification as filed for creating such a molecule which requires all of the amino acids outside the recited domains are substituted with non-conservative amino acids.

Claim 20 is directed to molecules wherein "the non-conservative substitutions are all of surface residues". There does not appear to be a basis in the specification as filed for creating such a molecule which requires all of the surface residues to be substituted with non-conservative amino acids.

Claim 23 is directed to molecules wherein "each non-conservative substitutions is with a replacement amino acid found a the corresponding position in a vertebrate growth hormone, prolactin, placental lactogen, or other hormone homologous to human growth hormone". However, there is no teaching or disclosure in the specification of using amino acids from prolactin, placental lactogen, or other hormone homologous to human growth hormone in making

variants of growth hormone, therefore, this inventive concept does not find support in the specification as filed.

Claim 29 has been amended to include the recitation of "comprising residues corresponding to residues 96-133 of bovine growth hormone", for which there does not appear to be support in the specification. The instant specification does not contemplate a DNA molecule encoding a growth hormone receptor antagonist which comprises residues 96-133 of bovine growth hormone and is 50% identical to a reference vertebrate growth hormone, and therefore this inventive concept was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 30-33 depend from claim 29, therefore, they are also indefinite for this recitation.

Claim 34 recites a molecule "which has an ED50 which is less than about 10 times the ED50 of the first reference vertebrate growth hormone in an assay", which is not supported in the instant specification as filed. The specification does not support making a molecule which has the claimed function, therefore, the specification does not describe this inventive concept.

Claims 10, 29, 35, and 62 include a proviso which excludes a group of substitutions. However, there is no basis in the instant specification for this group of substitutions, and therefore, there is no basis for their exclusion. This is clearly new matter, and should be deleted from the claims.

Claim 37 recites that the substitution of Gly 119 is with an amino acid other than proline. There does not appear to be a basis for this negative limitation in the specification.

Claim 38 recites "which substitute amino acid has a greater alpha helical propensity than did the corresponding residue of said reference vertebrate hormone". However, the only mention of "alpha helical propensity" that could be found in the specification was at page 22, lines 11-14. There is no mention of substitution with a greater degree of propensity, but only that DNA which is degenerate should be prepared to encode amino acids with "acceptable alpha-helical propensities". Therefore, this appears to be an new inventive concept which does not find basis in the specification as filed.

7. Claims 10-44, 62, 65-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of a polypeptide which is a growth hormone receptor antagonist wherein the amino acid position of Gly 119 of bovine growth hormone is substituted with an amino acid other than glycine or alanine. The instant specification also provides for an analogous mutation in human growth hormone as well as for some additional modifications in the region of amino acid positions 115-125. The subject matter which is claimed is directed to non-naturally occurring polypeptides which have at least 50% sequence identity to "a first reference vertebrate hormone", have a

substitution which corresponds to amino acid position 119 of bovine growth hormone, and can be as short as 50 amino acids in length. First, a determination of the level of predictability in the art must be made in that whether the level of skill in the art leads to a predictability of structure; and/or whether teachings in the application or prior art lead to a predictability of structure. The claims are directed to non-naturally occurring polypeptides which share at least 50% identity to a "reference vertebrate hormone". First, the claims are not limited to those mutations which are exemplified in the instant specification. Although the specification contemplates making various other mutations in the growth hormone molecule, the specification does not provide mutating up to 50% of a polypeptide to generate a growth hormone receptor antagonist. Additionally, the instant specification does not provide for making a polypeptide with as few as 50 amino acids, which is also claimed. The specification only describes a handful of substitutions which provide the biological activity required by the claims and fails to teach or describe modifications which are commensurate in scope with the instant claims.. Therefore, there is a lack of guidance or teaching regarding structure and function because there are only very limited examples provided in the specification and because there is no guidance found in the prior art which is commensurate in scope with the claims.

Next in making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, each claimed species and genus must be evaluated to determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed. With this regard, the instant application fails to provide a written description of the species or the

genus which are encompassed by the instant claims except for the specific mutations which are provided in the examples of the specification which are limited to a very small portions of the growth hormone molecule. The specification does not provide a complete structure of those polypeptides which would be growth hormone receptor antagonist molecules as required by the claims. The claims also fail to recite other relevant identifying characteristics (physical and/or chemical and/or functional characteristics coupled with a known or disclosed correlation between function and structure) sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. The specification fails to provide a representative number of species for the claimed genus and the specification teaches a very limited number of embodiment. Therefore, the claims are directed subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues that the prior art discloses that a fragment of growth hormone comprising residues 96-133 is all that is required for biological activity. However, the instant claims do not require the presence of these amino acids (and the claim that includes this limitation is not supported in the instant specification as filed). Additionally, the instant claims provide for the mutation of these amino acids, for which there is no guidance in the specification. The issue at hand is that the specification is not commensurate in scope with what is being claimed and does not provide a written description of a sufficient number of species to support the genus that is being claimed.

Applicant argues that only 20% of the original growth hormone molecule is retained in the 96-133 amino acid fragment. However, the instant claims do not define the amino acids which are required for the biological activity which is claimed, and therefore, the recitation of 50% identity is not sufficient structure to provide the required function. The inclusion of the limitation of amino acids 96-133 in claim 29 is not supported by the specification as filed, and therefore, does not remedy this deficiency. Applicant argues that claim 74 requires the presence of 4 helices, but because this claim depends from a claim which only requires 50% identity, the amino acid composition of those helices is not clear. The instant specification only provides examples of mutations of a limited number of positions (115-125), and this does not support the breadth of the claims for mutating as much as 50% of the molecule, including "non-conservative" amino acid substitutions.

Applicant argues at page 5 of the response that guidance is provided for modifying the growth hormone protein "with a reasonable expectation of success of retention of receptor binding activity". However, this argument is not persuasive because most of the limitations of the claims are not supported by the specification as filed (new matter). Additionally, the examples which are provided in the specification do not support the breadth of the claims (written description). It is not clear how Applicant can indicate that a reasonable expectation of success exists for mutating as much as 50% of growth hormone in the manner that is claimed when the specification and the prior art do not provide a single example which is commensurate in scope with the claims. The fact that the specification and the claims do not identify those amino acid residues that are critical for activity would lead one of ordinary skill in the art to undue

experimentation in making molecules which meet the structural limitations of the claims, but fail to provide for the function of the claims. With all of the guidance that Applicant has enumerated in the response, one of ordinary skill in the art would still not have a reasonable expectation that any one embodiment that meets the structural limitations of the claims would provide for the function, absent evidence to the contrary. Applicant argues at page 6 of the response that substantial mutations may be made in a vertebrate GH without loss of vertebrate GH receptor binding activity. This statement does not appear to be supported by any facts of record. As pointed out above, the examples which are found in the specification are very limited and do not support the breadth of the claims.

Applicant argues at page 7 that mutations to growth hormone are additive. However, in the studies that were identified, it was not known what the biological effect of any particular mutation was going to have until the mutation was made. And even then, replacement with an amino acid which is "conservative" does not have a predictable result. The studies which are referenced still do not support the breadth of what is being claimed - indiscriminate mutation of as much as 50% of the growth hormone molecule with the expectation of receptor antagonist activity. Neither the specification nor the prior art support the breadth of what is being claimed.

Applicants arguments at page 8 are directed to combinatorial libraries. However, this argument is basically make and test, which is not the standard of enablement under 112. Applicant notes that a claim is not invalid because it reads upon some inoperative embodiments. However, the claims must be commensurate in scope with the disclosure in the specification, which is not the instant case. Applicant argues at pages 9-10 that prior patents which use %

identity and activity language are relevant and should be considered. However, each application is examined on its own merits and claims cannot be allowed purely on the presence of such claims in other patents. Applicant asserts that the Examiner stated that it was the practice of the PTO "to ignore prior allowances". This is a false statement. At page 6 of the previous Office action, it was stated that "it is not the practice of the PTO to allow claims based on previously allowed claims by the Office" because "each application is reviewed on its own merits". Therefore, prior allowances are not ignored, however, they also do not dictate the examination of subsequent applications.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 10-44, 62, 65-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-44, 62, 65-74 are indefinite with respect to the term "reference vertebrate growth hormone". This term is nowhere defined in the specification and does not have a well-known art-recognized meaning. Therefore, one cannot determine the metes and bounds of the claimed polypeptide.

Claim 39 recites "said helix corresponds to the third alpha helix of bovine growth hormone". This recitation is unclear because the claim from which it depends refers to "an alpha helix" which is from a "said reference vertebrate growth hormone". If claim 39 does not require

the reference vertebrate growth hormone to be bovine in nature, it is not clear how the helix could be bovine in nature. The claim should require the helix to be the third alpha helix and the reference hormone to be bovine in order to clearly understand what is being claimed.

Claim 63 is a method which depends from claim 46, which is canceled. Because there are no other method claims in the instant application, it is not clear what this claim encompasses. Therefore, the claim is indefinite and cannot be examined with regard to enablement, written description, or art issues.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January 28, 2000

CHRISTINE SAOUD
PATENT EXAMINER

Christine Saoud